Vitreous proteomics correlates with gene expression profile of uveal melanoma

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Disclosures

• **PM**: Castle Biosciences, Aura Biosciences, Arix Biosciences

• **VBM**: X-37, Takeda, Retinagenix, MantraBio, Ayoxxa, Protagonist, Spark Therapeutics, Guidepoint, 23&Me, Regeneron, Syncona, Vistra, Johnson & Johnson, GLG, Gyroscope, MeiraGTX
SUMMARY: PROTEOMICS APPROACH TO UM

- Detection without direct tumor biopsy
- GEP and PRAME based
- New targets
- Repurposed therapies
Metastatic disease is still the problem

- Up to 50% of Uveal Melanoma patients will develop metastatic disease
  - No change in survival
  - No approved or adjuvant therapy (sunitinib)
ESTIMATING METASTATIC RISK IS IMPORTANT

- Clinical features
- Histopathologic features
- Chromosomal alterations
  - High risk: 1p-, 6p-, +8q, -3
  - Low risk: +6p, 9p-
- Gene expression profiling
- PRAME expression

JUST BECAUSE I KNOW I HAVE A CLASS 2 MELANOMA..

- Unable to detect micrometastatic disease in the blood
  - *Circulating tumor cells in 34-46%*
  - *CTCs in 58% and cfDNA in 26%*

- No FDA or clinically actionable agents to treat

Anand et al. Cancers 2019,
Beasley et al. JCO Precision Oncology 2018
FROM GENOMICS TO PROTEOMICS
Central hypothesis
Eye fluid and serum protein signatures can provide early targeting of metastatic risk in UM.
PROTEOMICS IN UVEAL MELANOMA

PURPOSE:
To identify proteomic signatures in UM vitreous that correlate with GEP signatures

- Lacking shotgun approach
METHODS: IRB APPROVED PROSPECTIVE BIOREPOSITORY STUDY

• Plaque placement:
  • 27 g 3-port Diagnostic vitrectomy, aqueous biopsy, tumor sample

• Enucleation
  • Vitreous and aqueous fluid aspiration

• GEP/PRAME
  • Castle Biosciences

MOBILE OR LABORATORY INTERFACE (MORLI)
PROTEOMICS PIPELINE FOR PRECISION HEALTH

RESULTS: STUDY POPULATION

- 8 subjects with uveal melanoma
  - Mean age 53.9 years.
  - no ciliary body involvement
  - mean thickness 6.6mm.
- GEP:
  - Class 1A (3 eyes), Class 1B (2 eyes), Class 2 (3 eyes)
- PRAME expression was positive in 4 (50%)

+ 3 CONTROL ERM VITRECTOMY SAMPLES
PROTEIN BIOMARKER DISCOVERY PIPELINE

Principal Component Analysis (PCA)

Results:
Protein signatures can distinguish choroidal melanoma from control vitreous.
Results:

Proteomic signatures can distinguish molecular classes of choroidal melanoma.
TARGETED PROTEOMICS PLATFORMS

Conventional Test
1 protein

“Proteomics” Test
100-1000 proteins

Expression: 62 elevated
15 decreased

by multiplex ELISA

- **GEP class**
  - 46 differentially expressed proteins

- **PRAME expression**
  - 32 differentially expressed proteins
    
    \[
    (p < 0.01)
    \]
SHOTGUN PROTEOMICS SCREEN

20 CANDIDATE PROTEINS

- Validation in additional 11 UM samples and paired serum
- Identification of GEP and PRAME associated targets
REPURPOSED FOR CHOROIDAL MELANOMA?

- Using protein signatures to target metastatic risk biology with current FDA approved drugs

*Therapeutic drug repositioning using personalized proteomics of liquid biopsies*

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**Future Directions: Melanoma Proteomics**

- Expanded validation
- Serial serum and metastatic tumor
- Plausibility of repurposed agents in adjuvant trials
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